学位論文の要旨

Age, Dehydration, Respiratory Failure, Orientation Disturbance, and Blood Pressure Score Predicts In-hospital Mortality in HIV-negative Non-multidrug-resistant Smear-positive Pulmonary Tuberculosis in Japan

(日本での塗抹陽性、非多剤耐性、HIV 陰性の肺結核入院患者に対して、ADROP スコアが生命予後予測に有用であるかの検討)

Kenjiro Nagai

長井　賢次郎

Department of Pulmonology, Yokohama City University Graduate School of Medicine, Yokohama, Japan.

横浜市立大学　大学院医学研究科　呼吸器病学教室

(Doctoral Superior: Takeshi Kaneko, Professor)
指導教員：金子　猛　教授

学位論文の要旨

Age, Dehydration, Respiratory Failure, Orientation Disturbance, and Blood Pressure Score Predicts In-hospital Mortality in HIV-negative Non-multidrug-resistant Smear-positive Pulmonary Tuberculosis in Japan

（日本での塗抹陽性、非多剤耐性、HIV 陰性の肺結核入院患者に対して、ADROP スコアが生命予後予測に有用であるかの検討）

Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is an infectious disease that has adversely affected human beings for many centuries. (Lonnroth., K. & Raviglione. M,2008).

The Japanese Respiratory Society has proposed 6-point scale (0–5) to assess the clinical severity of CAP; Age, Dehydration, Respiratory failure, Orientation disturbance, and blood Pressure (A-DROP). (Matsushima T,2005).

The purpose of this retrospective study was to determine whether A-DROP could predict the risk of death in patients with pulmonary TB.

Materials and Methods

Patients

The study was a retrospective cohort study of in-patients admitted to Yokohama City University Hospital. The patient records were reviewed from April 2007 to May 2015 on the basis of the admission. All the consecutive patients admitted to the isolation wards with a primary diagnosis of pulmonary TB and satisfying the inclusion criteria were reviewed.

The inclusion criteria were as follows: (i) active smear-positive pulmonary TB diagnosed with sputum culture and smear, (ii) newly diagnosed disease (patients who had already started treatment in another hospital were excluded), (iii) age ≥ 15 years on admission, and (iv) admission after TB diagnosis.

Exclusion criteria were (i) HIV positive status, (ii) MDR-TB, i.e. resistance to both isoniazid and rifampicin, (iii) transferred out, i.e. patients moved to another

facility before the negative infectivity was confirmed, (iv) treatment failure that was defined by the persistent smear positivity after 12 months of admission (Laserson, K. F., et al,2005).

We evaluated the patients' severity at admission using the A-DROP score (Shindo, Y., et al,2008). All components of the A-DROP score were clearly described in the chart on admission.

The A-DROP scoring system assesses the following parameters: (i) Age (men ≥ 70 years, women ≥ 75 years); (ii) Dehydration (blood urea nitrogen ≥ 21 mg/dL); (iii) Respiratory failure (arterial oxygen saturation ≤ 90% or arterial oxygen pressure ≤ 60 mm Hg); (iv) Orientation disturbance (confusion); and (v) blood Pressure (systolic blood pressure ≤ 90 mmHg).(Shindo, Y., et al,2008, The Japanese Respiratory Society, 2005).

Statistics

Fisher's exact test and a Mann-Whitney rank sum test were used for binary variables and continuous variables, respectively. The receiver operating characteristics (ROC) curve and area under the ROC curve (AUC) were used to evaluate the predictive ability of the A-DROP score for in-hospital death. A Kaplan-Meier curve and log-rank test were used to compare the survival of patients with each A-DROP score. For the Kaplan-Meier curve analysis, patients were censored when discharged alive. Univariate logistic regression analysis was used to estimate how a one-point increase in the total A-DROP score affected in-hospital mortality. Multiple variate logistic regression analysis was used to estimate how each component of the A-DROP score affected in-hospital mortality. The Cox proportional hazard model was used to calculate the hazard ratio (HR). Medians are presented with the interquartile range (IQR).

All analyses were performed using GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA) and Excel Toukei 2012 (SSRI, Tokyo, Japan).

Results

The cohort consisted of 134 men (38.8%), 211 women (61.2%), 272 who discharged alive (28.8%), and 73 who died in-hospital (21.2%) with a median age of 72 (IQR: 54-82) years. A one-point increase in the A-DROP score was associated with a higher risk for in-hospital mortality with odds ratio of 3.8 (95% confidence interval 2.8-5.2, $P<0.001$). The area under receiver operating characteristics curve was 0.86. The total score cutoff

of 1.5 provided the best Youden Index of 0.61. Using this criteria, total score > 1.5, sensitivity was 85% and specificity was 76%. Kaplan-Meier curve clearly indicated that in-hospital mortality increased with higher A-DROP scores (Log-rank test <0.001).

Discussion

We retrospectively revealed that the A-DROP score effectively determines all-cause in-hospital mortality in HIV-negative non-MDR smear-positive TB. Sensitivity analyses based on treatment regimen and different outcome, i.e. in-hospital death and 28-day death, ensured the robustness of the result. To our knowledge, this is the first study that has evaluated the prognostic ability of the A-DROP score for TB cases while previous studies evaluated CAP patients. The study results showed that each component of the A-DROP score, except for low blood pressure, along with the total A-DROP score had good predictive ability for in-hospital mortality for TB patients. We think the A-DROP score is useful when physicians treat TB patients for some purposes. First, the scoring system let us know which patients needed close monitoring during their hospital stay. Second, knowing the poor prognosis, patients, family, and physicians can discuss advanced directives concerning the intensive treatment. Some patients, especially the elderly, do not like to have intensive care such as mechanical ventilation [5,6]. Third, having an accurate prognosis of patients enables physicians to provide accurate information to patients. Provision of sufficient information is particularly important for admitted smear-positive TB patients because they usually have anxiety about the long-term hospitalization (Moussas, G., et al,2008). In conclusion, A-DROP score clearly indicate pulmonary tuberculosis in-hospital mortality.

References

Goodman, M. D., Tarnoff, M., & Slotman, G. J. Effect of advance directives on the management of elderly critically ill patients. *Crit Care Med.* **26**,701-704 (1998).

Laserson, K. F., et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int. J. Tuberc. Lung. Dis.* **9**, 640-645 (2005)

Lonnroth., K. & Raviglione. M. Global epidemiology of tuberculosis: prospects for control. *Semin. Respir. Crit. Care. Med.* **29**, 481-491 (2008).

Moussas, G., et al. A comparative study of anxiety and depression in patients with bronchial asthma, chronic obstructive pulmonary disease and tuberculosis in a general hospital of chest diseases. *Ann Gen Psychiatry.* **7**,7 (2008).

Shindo, Y., et al. Comparison of severity scoring systems A-DROP and CURB-65 for community-acquired pneumonia. *Respirology.* **13**, 731-735 (2008). Shindo, Y., et al.

The Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adult (ed Matsushima T) Ch. 6, 10-11 (The Japanese Respiratory Society, 2005).

Tschirhart, E. C., Du, Q. & Kelley, A. S. Factors influencing the use of intensive procedures at the end of life. *J Am Geriatr Soc.* **62**, 2088-2094 (2014).

論　文　目　録

Ⅰ 主 論 文

Age, Dehydration, Respiratory Failure, Orientation Disturbance, and Blood Pressure Score Predicts In-hospital Mortality in HIV-negative Non-multidrug-resistant Smear-positive Pulmonary Tuberculosis in Japan

Kenjiro N, Horita N, Yamamoto M, Sato T, T, Nagakura H, Kaneko T.

Sci Rep, 2016 . [In press]

Ⅱ 副 論 文

Ⅲ 参 考 文

1. A case of IgG4-related disease with deterioration in pulmonary and pituitary involvements during a 10-year clinical course of inflammatory pseudotumor

Nagai K:Nihon Kokyuki Gakkai Zasshi.2011 Dec;49(12):922-8

2. PET/CT Findings for Bone Marrow Carcinosis Because of Lung Adenocarcinoma

Keisuke Watanabe, MD, Masaharu Shinkai, MD, PhD.,Kenjiro Nagai, MD,Nobuhiro Yamaguchi,MD, Yoshiaki Ishigatsubo, MD, PhD, and Takeshi Kaneko, MD, PhD

Journal of Thoracic Oncology:Volume 8, Number 11,November 2013

3. Amrubicin for relapsed small-cell lung cancer: a systematic review and meta-analysis of 803 patients.

Horita N, Yamamoto M, Sato T, Tsukahara T, Nagakura H, Tashiro K, Shibata Y, Watanabe H, Nagai K, Nakashima K, Ushio R, Ikeda M, Kobayashi N, Shinkai M, Kudo M, Kaneko T.

Sci Rep, 2016.

4. Sensitivity and specificity of Cobas TaqMan MTB real-time polymerase chain reaction for culture-proven Mycobacterium tuberculosis: meta-analysis of 26999 specimens from 17 Studies.

Horita N, Yamamoto M, Sato T, Tsukahara T, Nagakura H, Tashiro K, Shibata Y, Watanabe H, Nagai K, Nakashima K, Ushio R, Ikeda M, Sakamaki K, Yoshiyama T, Kaneko T.

Sci Rep, 2015. [In press]

5. Topotecan for Relapsed Small-cell Lung Cancer: Systematic Review and Meta-Analysis of 1347 Patients.

Horita N, Yamamoto M, Sato T, Tsukahara T, Nagakura H, Tashiro K, Shibata Y, Watanabe H, Nagai K, Inoue M, Nakashima K, Ushio R, Shinkai M, Kudo M, Kaneko T.

Sci Rep. 5: 15437, 2015.